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Congenital Malformations: Prenatal Diagnosis and Management

Ahmed Bashir*

Department of Pediatrics Jubail, KSA

***Corresponding author:** Ahmed Bashir, Al Mana General Hospital, Department of Pediatrics Jubail, KSA.

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Introduction

Congenital malformations are estimated to be 2-4% of all births. Despite their relatively low prevalence, fetal malformations are responsible for approximately 30% of perinatal deaths, and considerable infant morbidity in developed countries [1]. Fetal malforml formations can be defined as structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth or later in life.

Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations. Congenital disorders are the major cause of new born deaths within the perinatal peroid, which can result in long-term disability with a significant impact on individuals, families, societies and health-care systems [2]. Prenatal diagnosis of congenital disease provides information for decisions during pregnancy and appropriate treatment parentally (timed delivery in tertiary care centers), it is assumed to improve perinatal and longterm outcome. However, this assumption has been demonstrated only for few specific subsets of malformations, and with conflicting results [3] showed that prenatal diagnosis reduced the overall pre- and post-operative mortality in fetuses affected by complete transposition. In another study [4]. preoperative conditions were improved in cases with complete transposition and hypoplastic left heart, without improvement in perinatal mortality. At 2 years the survival was the same in diagnosed as in undiagnosed fetuses with pulmonary Artesia with intact ventricular septum [5]. No improvement was seen in cases of hypoplastic left heart diagnosed antenatally versus postnatally [6]. Prenatal diagnosis, (discovered Over the last two decades) has greatly benefited from advances in ultrasound technology and in our ability to detect microscopic and submicroscopic chromosome abnormalities as well as single gene disorders, leading to substantive improvements in detection of such congenital anomalies. At present, invasive prenatal diagnosis continues to be the gold standard for pregnancies at increased risk for chromosomal anomaly or other genetic disease, with chorionic villus sampling being the procedure of choice for the first trimester. Whereas mid- trimester amniocentesis continues to be the most common form of invasive procedure for prenatal diagnosis [7]. Still, invasive techniques are restricted to subgroups at risk for anomalies; such time-consuming procedures are believed to be cost-effective, also accounting for procedure-related abortive risks. In the low-risk population prenatal diagnosis generally consists of screening procedures by means of ultrasound and maternal serum biochemistry. A major impact of antenatal diagnosis of malformations is related to the severity of the malformations detected. Most severe defects are reportedly detected earlier than minor ones, which is especially relevant in many countries where only before viability is termination of pregnancy authorized by law [8].

The potential of ultrasound for detecting structural malformations were derived from populations at specific risk investigated, the data showed that the sensitivities are as high as 85-90%. Those data could not be replicated in the general population. The detection rates data using ultrasound for screening for fetal malformations do vary widely, showing a range from 8.7% to 85% [9]. Such wide differences reflect varying criteria for definition of malformation, postnatal examination, selection of study population, prevalence of specific anomalies within a population, and other methodology issues (e.g., single hospital versus multicenter setting, expertise and skills of operators, use of standardized protocols for ultrasonographic examination [10]. Ultrasound imaging is now routinely used in most European and North American countries for the purpose of screening pregnancies for fetal malformations. The modalities, reliability and value of such screening in each country, however, are controversial.

Specific anomalies, such as agenesis of corpus callosum, posterior fossa cysts, cerebral cleft, and migrational disorders such as lissencephaly, could be investigated by Magnetic resonance imaging [11]. Use of Magnetic Resonance Imaging is nonetheless uncommon in clinical practice, being restricted to specific

indications [12]. It should be first noted that most structural anomalies are increasingly detected with advancing gestation [8]. In early pregnancy, it is possible to recognize with confidence certain types of fetal malformations, like anencephaly, which can be reliably diagnosed at 10-14 weeks of pregnancy [13]. In some cases, omphalocele and limb anomalies are also definable using ultrasound in the first trimester, while other structural anomalies, like urinary tract abnormalities, are detectable later in pregnancy [14]. Screening for neural tube defects may ideally involve ultrasound examination in conjunction with maternal serum alpha-fetoprotein screen [12]. On comparison of the two methods, maternal serum screening was found to have a slightly greater sensitivity compared to ultrasound [15].

Ultrasound screening for fetal structural abnormalities is generally recommended at 19-21 weeks of gestational age. The accuracy in detecting malformations by ultrasound, however, shows great variability among centres and operators. Nonetheless, the overall sensitivity for ultrasonographic ally detectable fetal malformations was 35% in tertiary facilities significantly higher compared to 13% in community hospitals, suggesting that operator experience, skills, and training are important determinant [10]. Other factors affecting sensitivity are single vs multicentre study, type of malformation (major vs minor, single vs multiple, natural history of the disease during fetal life), gestational age at ultrasound examination, length and accuracy of follow-up (some malformations are detected in early or even late infancy) [16].

Ultrasound screening at 10-14 weeks has included measurement of nuchal translucency, (which is the maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine of the fetus) [17]. An increased nuchal translucency is associated with aneuploidy and cardiac malformations [18].

Combined with ultrasound results or alone, maternal serum biochemistry is a valid tool used for screening for chromosomal anomalies toward the end of the first trimester or in the early midtrimester [19]. Use of second trimester ultrasound for detection of chromosomal anomalies was first suggested in 1985 [20]. Chromosomal defects were progressively found to be associated with certain sonographic features, including biometric parameters (e.g., short length of femur and humerus, pyelectasis, large nuchal fold, ventriculomegaly, early fetal growth restriction) and morphologic signs (e.g., choroids plexus cysts, echogenic bowel, echogenic intracardiac focus). Their reliability is undoubtedly increased in pregnant women at increased risk for Down syndrome, but the positive predictive value for each marker is dramatically decreased in low-risk women when applying the Bayes' theorem [21].

"Down syndrome markers" make up a heterogeneous group, including common findings in normal fetuses, like the echogenic intracardiac focus which occurs in approximately 5% of fetuses. As a result, ultrasound soft markers lead to a small increase in detection of congenital anomalies but a large increase in false positives. The detection of any of the above markers during a routine sonogram warrants careful scanning aimed at identifying additional markers because the finding of multiple markers indicates high risk for chromosomal anomaly [22]. Computerised programmes have been developed which permit to estimate the adjusted risk for aneuploidy by combining background risk (based on maternal age) and biochemical screening together with the above ultrasound features [23].

These are useful when a marker is a chance finding during routine ultrasound scanning., At present, in the absence of studies validating second trimester sonography for the purpose of screening the general population for chromosomal anomalies, such use of ultrasound is not a recommended procedure [24]. For example, it has been shown that the inclusion of soft markers when screening at 20 – 22 weeks improves the detection rate of malformations from 50% to 54%; however, it also increases the number of false positive results from 0.04% to 0.53% Boyd PA et al. [25] studied two terminations of pregnancies carrying unaffected fetuses were performed. Moreover, the finding of a marker may adversely affect the pregnancy due to anxiety caused to the mother [26].

Structural congenital heart disease (CHD) described in postnatal life has been detected in utero by fetal cardiac ultrasound.16 From published series of structural cardiac anomalies detected during fetal life it is apparent that the closest figure to the true incidence of CHD in the general population of fetuses is 1percent [27]. Prenatal and postnatal series discrepancies can be partly explained by the unexpectedly high tendency towards spontaneous intra-uterine demise and early postnatal death of fetuses with cardiac abnormalities [28]. It is clear that there is a strong association between the presence of fetal cardiac disease, extracardiac abnormalities and aneuplodies [29]. While the incidence of chromosomal abnormalities in fetuses with CHD ranges from 17 to 48 per cent, [29-32] only 5-10 per cent of infants with congenital heart disease are found to be chromosomically abnormal [33]. Associated extracardiac structural malformations are more frequent as well, i.e. 19% prenatally compared to 13% at birth in the largest Italian series [28].

This discrepancy is likely to be due to the tendency toward spontaneous fetal loss of pregnancies carrying chromosomically and/or structurally abnormal fetuses; however, it is difficult to prove it, because of the high pregnancy termination rate altering the natural history of disease. The recent reports by Paladini D, Rustico and others on 67 cases of anomalies of ventricular diagnosed prenatally: chromosomal aberrations and extracardiac malformations were found in 18% and 37%, respectively [34]. There were 48% livebirths in isolated cases and 15% in cases with extracardiac anomalies. The frequency of association with aneuploidies and/or extracardiac anomalies is different for differing congenital heart diseases, being highest for atrio-ventricular septal defects (48%) and lowest for complete transposition of the great arteries (concordant atrioventricular connections with discordant ventriculoarterial connections) (0-2.6%) [28,29].

Ultrasound screening for fetal cardiac malformations is part of routine ultrasound screening at 19-21 weeks, according to scanning protocols including the four-chamber view [27]. In the setting of a low-risk population, a four-chamber view of the fetal heart

potentially allows, at the best of its performance, the detection of only 40% of fetuses with complex heart disease [35] most missed cardiac lesions commonly involve outflow tract anomalies such as complete transposition, common arterial trunk, and aortic coarctation or minor anomalies such as atrial septal defects (septum secundum), small ventricles. The same considerations reported above for screening of congenital defects hold true for cardiac malformations, namely, different sensitivities for different settings and malformations [2,27,36]. Atrial septal defects, mild pulmonary or aortic stenosis [10,16,27]. Incorporating visualization of the outflow tracts and the great arteries into the scanning protocol would increase the detection rate to 65-70%.

However, data on this type of screening is still limited [37,38]. Fetal echocardiography should be performed in groups selected on the basis of patient history and sonographic anomalies or markers, including extracardiac anomalies, maternal diabetes, infection, suspicious scan on screening, chromosomal aberrations. In this context, also should be listed abnormal biochemical screening or maternal age older than 34 years coupled with refusal of invasive karyotyping, increased nuchal translucency, early onset (below 32 weeks) fetal growth restriction, fetal arrhythmias, family history of congenital heart disease, hydrops, exposure to teratogenic agents [16,39]. Estimates of diagnostic accuracy of fetal echocardiography depend on the prevalence of those anomalies which are most difficult to detect, like mild pulmonary stenosis, small septal defects, and aortic coarctation [40].

In the coming Future directions require the assessment of cost-effectiveness of screening ultrasound in differing settings in terms of populations and health care provision systems. A large, multicentre study of minor markers of Down syndrome is needed on low-risk patients to replace the data extrapolated from high-risk patient to the low- risk population [21,26]. Apart from methodological issues, our knowledge of certain conditions is to be improved. For example, screening ultrasonography has been shown to increase the frequency of prenatally diagnosed hydronephrosis. Many infants with congenital hydronephrosis remain without symptoms for months or even years before diagnosis, it should be important to establish whether prenatal diagnosis would benefit otherwise asymptomatic infants by preserving their renal function. The poorly understood and currently under investigation is the in-utero development of some types of congenital heart defects [41]. Further assessment is needed for the incorporation of visualization of outflow tracts into the ultrasound screening protocol for congenital heart disease [42].

Because ultrasound can detect associations of specific anomalies, detection of patterns of anomalies may help make a diagnosis or determine which pregnant women should be offered invasive testing. The specificity of associations of the most frequent patterns has been analyzed, and different patterns were found to aggregate in a relatively small number of clusters, so that several patterns can be considered in non-random associations [43]. Proper analysis of antenatal sonographic data sets might enable detection of new patterns of associations of anomalies, enhancing further the diagnostic potential of the test. It is difficult to establish to what extent information provided by Magnetic Resonance Imaging may warrant changes in patient counselling and management, so that further studies are needed to assess how additional information from MRI may affect outcome [44-56]. In the meantime, real-time fast acquisition MRI methods are being developed.

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